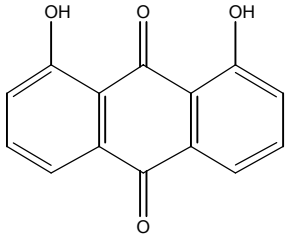
DANTHRON (1,8-DIHYDROXYANTHRAQUINONE)
CAS No. 117-10-2
First Listed in the *Eighth Report on Carcinogens*



CARCINOGENICITY

Danthron is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of malignant tumor formation in multiple species of experimental animals (IARC V.50, 1990). When administered in the diet to male rats, danthron induced adenomas and adenocarcinomas of the colon and adenomas of the cecum. When administered in the diet to male mice, danthron caused an increase in the incidence of hepatocellular carcinomas.

There are no adequate data available to evaluate the carcinogenicity of danthron in humans.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Danthron has been evaluated in studies for its ability to enhance the expression of tumors induced by other chemicals. When danthron was administered in the feed to mice that also received 1,2-dimethylhydrazine, the incidence and multiplicity of adenomas of the colon and liver were significantly increased (Sugie et al., 1994). When evaluated in skin painting studies in mice given 7,12-dimethylbenz[*a*]anthracene, or in rats given 1,2-dimethylhydrazine, danthron gave negative results (IARC V.50, 1990). When administered in the diet without other chemicals, danthron caused a large increase in the incidence of a preneoplastic lesion, adenomatous polyploid hyperplasia of the cecum and colon in male mice. Danthron has been found to induce genetic damage in a limited number of prokaryotic, lower eukaryotic, and mammalian *in vitro* test systems.

No data are available that would suggest that the mechanisms thought to account for tumor induction by danthron in experimental animals would not also operate in humans.

PROPERTIES

Danthron occurs as an orange crystalline powder or as red or reddish-yellow needles or leaves. It begins to sublime at approximately 75 ^{o}C and has a melting point of 190-197 ^{o}C. Danthron is very soluble in aqueous alkali hydroxides; soluble in acetone, chloroform, diethyl ether, and ethanol; and almost insoluble in water. When heated to decomposition, it emits acrid smoke and irritating fumes.

USE

Danthron has been widely used since the beginning of this century as a laxative (IARC V.50, 1990). However, the FDA ordered its withdrawal from the market for this purpose in 1987 (58 FR 46589, 1993), and U.S. manufacturers voluntarily withdrew production of all human drug products containing the compound (IARC V.50, 1990). It is currently used as an antioxidant in synthetic lubricants, in the synthesis of experimental antitumor agents, and as a fungicide for control of powdery mildew (HSDB, 1996). It is also used, to a lesser extent, as an intermediate in the manufacture of dyes and forms lakes with calcium, barium, and lead (Kirk-Othmer V.11, 1980).

PRODUCTION

Danthron is synthesized in Germany, India, Japan, Poland, the United Kingdom, and the United States (IARC V.50, 1990). The *Directory of Chemical Producers*, however, lists no current producers for danthron, but it did report that one U.S. company produced an unknown quantity of it in 1992 (SRIa, 1997, 1992). The 1998 Chemical Buyers Directory and Chemcyclopedia 98 do not identify any current domestic suppliers of the chemical (Tilton, 1997; Rodnan, 1997). In 1996, 17 U.S. suppliers of danthron were identified (Chem Sources, 1996). The TSCA inventory for U.S. plants and producers listed 8 plants that produced or imported danthron in 1977. Three of the 8 were known manufacturers, 3 were known importers, and it was not known whether the other 2 were importers or manufacturers. The order of magnitude of the production volume was given for only one known manufacturer (100,000 to 1,000,000 lb/year). One producer or importer handled 1,000 to 10,000 lb/year. Two of the 3 known producers did not ship danthron out of the plant; i.e., its production and use were site-limited (TSCAPP, 1983 update). No data on imports or exports of danthron were available. In 1987, about 40 small manufacturers of danthron-containing pharmaceuticals were directed by FDA to withdraw their products from the market (Diogenes, 1976-1996).

EXPOSURE

The primary route of potential human exposure to danthron is oral administration. Shortly before its withdrawal from the market, danthron was available from 9 companies in 14 over-the-counter (OTC) products with the following tradenames: Danivac, Doctate-P, Dorbane, Dorbantyl, Dorbantyl Forte, Doxan, Doxidan, Magcyl, Modane, Tonelax, West-Ward Dioctyl with Danthron, and Valax. Tablet formulations contained 37.5, 50, or 75 mg danthron; capsule formulations, 25, 40, or 50 mg; and a liquid formulation, 37.5 mg/5 mL (5 mL = 1 teaspoonful) (CTCP, 1985). Potential exposure of health professionals may occur during the preparation and administration of the compound. Potential occupational exposure may also occur for workers involved in the formulation and packaging of the pharmaceutical. The National Occupational Exposure Survey (1981-1983) indicated that 357 workers, including 187 women, were potentially exposed to danthron (NIOSH, 1990). This estimate was derived from observations of the use of the actual compound (47% of total observations) and tradename products (54%). The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 3,120 workers were potentially exposed to danthron in the workplace (NIOSH, 1976). Danthron occurs naturally in several species of plants and insects. It has been isolated from dried leaves and stems of *Xyris semifuscata* harvested in Madagascar and is the basic structure of the aglycones of naturally occurring laxative glycosides. The compound has been identified in larvae of the elm-leaf beetle, *Pyrrhalta luteola*. The presence of a mixture of anthraquinones and

anthrones was suggested to be a means of protection from predators, and these compounds appear to be biosynthesized by the insect (IARC V.50, 1990).

REGULATIONS

In 1987, the FDA published a letter and a press release to recall all danthron-containing drug products by about 40 small manufacturers. Larger manufacturers had voluntarily halted production before the advisement. Both publications are in OTC Vol. 090TFM2, Docket 78N-036L (58 FR 46589, 1993; Diogenes, 1976-1996).